PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

REC'D 28 APR 2006
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Applicant's or agent's file reference	FOR FURTHER ACTION	See Form PCT/IPEA/416
IB/G-33704A/BCK		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP2005/003332	30.03.2005	31.03.2004

International Patent Classification (IPC) or national classification and IPC
INV. C07D417/12 A61K9/16 A61P5/00

Applicant
SANDOZ AG et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 5 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☒ *sent to the applicant and to the International Bureau)* a total of 4 sheets, as follows:
      ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in celectronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the report
☐	Box No. II	Priority
☐	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☐	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☐	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☒	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27.01.2006	27.04.2006

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/EP2005/003332

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages	
1-16	as originally filed
Claims, Numbers	
1-24	received on 27.01.2006 with letter of 28.11.2005
Drawings, Figures	
1-25	as originally filed

   ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-24
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-24
Industrial applicability (IA)	Yes:	Claims	1-24
	No:	Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Box No. VIII Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:

see separate sheet

Re Item V. and VIII.

1. Reference is made to the following documents:
   D1 : US 6 248 363 B1 (PATEL MAHESH V ET AL) 19 June 2001 (2001-06-19)
   D2 : WO 02/26737 A (REDDY'S RESEARCH FOUNDATION; CORD, JANET, I; CHEBIYYAM, PRABHAKAR; MAM) 4 April 2002 (2002-04-04)

   In the light of the cited prior art documents the subject matter claimed appears to be novel as far as it can be considered as clear (Article 6 PCT) and to lack an inventive step (Articles 33(2) and (3) PCT).

   The subject matter claimed relates to coprecipitates and solid solutions of amorphous rosiglitazone maleate, a process for the preparation thereof, pharmaceutical compositions comprising them and their use. The term "coprecipitate" without further definition appears to be no technical feature whose chemical nature is immediately evident for a skilled person. It is considered to be unclear (Article 6 PCT, item VIII) and to emcompass all possible compounds which would precipitate together with rosiglitazone maleate, which can be side products exhibiting completely different structures. The term has been interpreted according to the description, where "coprecipitate" is defined as solid dispersion of amorphous rosiglitazone maleate and thus the search has been restricted to such dispersions.

   D1 refers to solid carriers for improved delivery of active ingredients in pharmaceutical compositions. In column 7, line 42 as active ingredient rosiglitazone is mentioned and in column 36, line 52 a coprecipitate of the active ingredient is mentioned. In D1 amorphous forms of rosiglitazone and the maleate thereof are not disclosed.

   D2 refers to pharmaceutical compositions in claim 9 of various forms of rosiglitazone maleates are disclosed.

2. The technical problem underlying the present application appears to have been the provision of a novel stable solid dispersion (coprecipitate) of amorphous rosiglitazone maleate or solid solution of rosiglitazone maleate.

The objection re inventive step is maintained. Without clear definition of the term "coprecipitate" the contribution of the subject matter claimed over the prior art cannot be determined and the solution of the tecnical problem cannot be assessed for the whole claimed range.

As to the subject matter claimed referring to "solid solution of rosiglitazone maleate" (claims 20-24) per se, process for its preparation and pharmaceutical composition containing it, the subject matter claimed is not directed to "amorphous" form of rosiglitazone but to "rosiglitazone maleate" which could therefore also be of crystalline nature, which would then be obvious over the cited prior art.

Claims

1. A coprecipitate of amorphous rosiglitazone maleate with a pharmaceutically acceptable carrier.

2. A coprecipitate of amorphous rosiglitazone maleate with a pharmaceutically acceptable carrier according to claim 1, wherein the carrier is selected from the group consisting of polyvinylpyrrolidone, silicium dioxide, mannitol, lactose, methylcellulose and cyclodextrin.

3. The coprecipitate according to claim 1, wherein it is the coprecipitate of amorphous rosiglitazone maleate with polyvinylpyrrolidone.

4. The coprecipitate according to claim 1, wherein it is the coprecipitate of amorphous rosiglitazone maleate with silicon dioxide.

5. The coprecipitate according to claim 1, wherein it is the coprecipitate of amorphous rosiglitazone maleate with mannitol.

6. The coprecipitate according to claim 1, wherein it is the coprecipitate of amorphous rosiglitazone maleate with lactose.

7. The coprecipitate according to claim 1, wherein it is the coprecipitate of amorphous rosiglitazone maleate with methylcellulose.

8. The coprecipitate according to claim 1, wherein it is the coprecipitate of amorphous rosiglitazone maleate with gamma-cyclodextrin.

9. A coprecipitate according to claims 1 to 8, wherein the ratio of amorphous rosiglitazone maleate to a pharmaceutically acceptable carrier ranges from 1 : 1 to 1 : 20 parts by weight.

10. A coprecipitate according to claims 1 to 8, wherein the ratio of amorphous rosiglitazone maleate to a pharmaceutically acceptable carrier ranges from 1 : 1 to 1 : 4 parts by weight.

11. A process for the preparation of a coprecipitate of amorphous rosiglitazone maleate with a pharmaceutically acceptable carrier according to any one of claims 1 to 10, which comprises the steps of:
    a) dissolving rosiglitazone maleate in an organic solvent or in an aqueous solution of organic solvent,
    b) adding pharmaceutically acceptable carrier,
    c) spray-drying the obtained solution.

12. The process according to claim 11, wherein a pharmaceutically acceptable carrier is selected from the group consisting of polyvinylpyrrolidone, silicon dioxide, mannitol, lactose, methylcellulose and cyclodextrin.

13. The process according to claim 11, wherein an organic solvent is selected from the group consisting of ethanol and acetone.

14. The process according to claim 11, wherein the range of organic solvent to water is from about 9 : 1 to about 1 : 1 (V / V).

15. The process according to claims 11, wherein the range of organic solvent to water is from about 9 : 1 to about 7 : 3 (V / V)

16. A process for the preparation of a coprecipitate of amorphous rosiglitazone maleate with a pharmaceutically acceptable carrier according to any one of claims 1 to 10, which comprises the steps of:
    a) dissolving rosiglitazone (base) in an organic solvent
    b) adding maleic acid and stirred the mixture to obtain a clear solution,
    c) adding pharmaceutically acceptable carrier,

d) spray-drying the obtained solution.

17. A pharmaceutical composition comprising a coprecipitate of amorphous rosiglitazone maleate with a pharmaceutically acceptable carrier according to any one of claims 1 to 10 and other excipients.

18. A coprecipitate of amorphous rosiglitazone maleate with a pharmaceutically acceptable carrier according to claims 1 to 10, for use in the treatment and / or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

19. The use of a coprecipitate of amorphous rosiglitazone maleate with a pharmaceutically acceptable carrier according to claims 1 to 10, for the manufacture of a medicament for the treatment and / or prophylaxis of diabetes mellitus, conditions associated with diabetes mellitus and certain complications thereof.

20. A solid solution of rosiglitazone maleate with a pharmaceutically acceptable carrier.

21. A solid solution according to claim 20, wherein the pharmaceutically acceptable carrier is selected from polyethylene glycols between 4000 to 40.000 of average mol. weight.

22. A process for the preparation of a solid solution of rosiglitazone maleate with a pharmaceuticall acceptable carrier according to claim 20, which comprises the steps of:

a) melting rosilitazone maleate or optionally rosiglitazone and maleic acid with a pharmaceutically acceptable carrier to form a melt
b) cooling the obtained melted solution

23. The process according to claim 22, wherein a pharmaceutically acceptable carrier is selected from polyethylene glycols between 4000 to 40.000 of average mol. weight.

24. A pharmaceutical composition comprising a solid solution of rosiglitazone maleate with a pharmaceutically acceptable carrier according to claim 20 and other excipients.